

Study Protocol

**Official Title: A Randomized Controlled Pilot Trial of Indomethacin
in Acute Pancreatitis**

ClinicalTrials.gov ID (NCT number): NCT02692391

Protocol Date: June 1st, 2013

Scientific Background

AP is an inflammatory disease with a highly variable clinical course that is potentially lethal. This disease is currently the leading cause of gastrointestinal-related hospital admissions in the United States and continues to rise in incidence. The inciting event leading to the development of AP is the premature activation of the digestive pro-enzyme trypsinogen to trypsin within pancreatic acinar cells, resulting in pancreatic auto-digestion and inflammation. Inflammation localized to the gland can subsequently progress to a systemic inflammatory response affecting distant organs.

Studies have revealed a key role for phospholipase A2 in propagating this inflammatory response by inducing the production of inflammatory mediators, including arachidonic acid metabolites. Elevated levels of phospholipase A2 have been found in the serum of patients with AP who develop severe complications, including pancreatic necrosis, shock, and OF. The in vitro inhibition of phospholipase A2 using NSAIDs has been evaluated as a potential treatment strategy for AP, with indomethacin shown to be the most potent inhibitor among 17 tested agents. NSAIDs also inhibit the interaction of neutrophils with endothelial cells, thus preventing the accumulation of neutrophils at the site of injury.

In animal models of AP, NSAIDs have been shown to attenuate AP severity and improve survival. Most human studies, however, have primarily assessed the role of NSAIDs in PEP prophylaxis. A meta-analysis of 4 randomized, controlled studies evaluating this effect revealed a protective role for these medications, and a recent multicenter, randomized controlled trial found that administering rectal indomethacin to patients at increased risk for PEP significantly reduced the incidence and severity of pancreatitis. In 1985, a small randomized controlled trial (n=30) of rectal indomethacin in patients with AP reported a significant decrease in the duration of pain. This is the only study to date evaluating NSAIDs following the onset of AP and did not evaluate systemic inflammation. The effect of rectal indomethacin in mitigating disease progression in patients at risk for developing severe disease thus remains to be evaluated. SIRS is a simple clinical score, ranging from 0-4, that utilizes objective, routine clinical parameters (body temperature, heart rate, respiratory rate or arterial carbon dioxide tension and white blood count) that directly reflect the underlying inflammatory response. The persistence of SIRS, defined by the presence of a SIRS score ≥ 2 at 48 hrs following presentation, has been shown to be significantly associated with the development of OF, pancreatic necrosis and death in patients with AP. Additionally, serum levels of CRP at 48 hours following admission have also been closely correlated with the development of OF.

Study Objectives

The predefined primary endpoint was the change in the SIRS score from randomization to 48h after the initial intervention, and to compare whether this change was different between subjects receiving rectal indomethacin and placebo. Secondary endpoints included (i) change in CRP levels from baseline to 48 hours, (ii) change in SIRS score at 24 and 72 hours, (iii) development of organ failure, (iv) AP severity, (v) length of hospital stay, and (vi) mortality. Other study outcomes included length of ICU stay, and PASS score at 24h, 48h, and 72h.

Study Design & Methods

This was a single-center, parallel-group, double-blind, randomized placebo-controlled trial conducted at the University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA.

Randomization and masking

Patients were randomly assigned in a 1:1 allocation ratio to either rectal indomethacin or placebo control within 72 hours of presentation to the emergency department. Simple non-block randomization was used. The randomization sequence was generated using computer-based random numbers and was only available to the central UPMC pharmacy to ensure allocation concealment. A 24-hour pharmacist was assigned to implement the randomization sequence, immediately after the study coordinator communicated the enrollment of a participant. Study participants, investigators, study coordinators, outcome evaluators, and care providers, were blinded to treatment assignment.

Study interventions

Patients randomized to the intervention arm received a loading dose of two 50-mg indomethacin suppositories, which was administered by the registered nurse assigned to the patient's care team. This was followed by five maintenance doses of 50-mg rectally administered at intervals of 8 hours for a total of 48 hours and up to six doses. The rectal route was used based on previous data demonstrating more rapid and complete availability of the drug as compared to oral administration.(3) Patients in the placebo arm received at similar intervals glycerin suppositories identical in shape, size, color, and packaging to the indomethacin group. All patients were co-administered a daily dose of intravenous 40-mg pantoprazole for gastrointestinal prophylaxis. Otherwise, all patients received conventional management according to standards of care of AP in the United States.(4, 5)

Data Collection

Data on demographics, comorbidities, etiology, history of AP, and transfer status, were recorded at the time of randomization. SIRS score (0-4) was calculated upon randomization and at 24h, 48h, and 72h from the time of initial intervention. The levels of C-reactive protein (CRP) were measured at the time of randomization and at 48h from the initial intervention. Other clinical outcomes and treatment strategies were evaluated daily until the end of the hospitalization. The development of organ failure (OF) was defined as a score ≥ 2 for cardiovascular, respiratory or renal systems, using the Modified Marshall Scoring System.(6) Duration of organ failure for over 48h was defined as persistent OF. Severity of AP during the hospital admission was categorized as mild, moderately-severe, and severe based on the Revised Atlanta Classification.(7) Daily recorded data was used for post-hoc calculation of the pancreatitis activity scoring system (PASS) at baseline and daily post-intervention.(8) This score is the summation of the following five parameters: organ failure ($\times 100$ per organ), oral intolerance ($\times 40$), systemic inflammatory response syndrome (SIRS) ($\times 25$ per criterion), morphine equivalent dose (MED) ($\times 5$), and pain score ($\times 5$). Detailed information on fluid resuscitation within the first 24h was obtained from medical records. Abdominal computed tomography (CT) was obtained at the discretion of the care providers, and was interpreted by expert abdominal radiologists, who were blinded to the study arm. If more than one CT scan was performed during

the admission, the one obtained closest to the third day of presentation was used to report the presence of pancreatic and peripancreatic necrosis.

The development of adverse events (AEs) was monitored by the study coordinator on a daily basis during the hospitalization. Any major AEs were reported to the IRB and DSMB. These reportable AEs included gastrointestinal bleeding, perforated viscus, acute kidney injury (increase in serum creatinine ≥ 0.3 mg/dL within 48 hours), allergic reaction, myocardial infarction, and death.

Eligibility Criteria

Adult subjects (≥ 18 years of age) admitted to UPMC with a diagnosis of AP were assessed for eligibility. Acute pancreatitis was defined based on at least two of the following criteria: abdominal pain characteristic of AP; serum amylase and/or lipase greater than 3 times the upper limit of normal; or characteristic findings of AP on cross sectional images.(1) Patients with SIRS within the first 72 hours (h) of initial hospital presentation were eligible for randomization. SIRS was defined by the presence of two or more of the following criteria: a) pulse >90 beats/min; b) respiratory rate >20 /min or PaCO₂ <32 mmHg; c) temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; and d) white blood cell count $>12,000$ or <4000 cells/mm³ or $>10\%$ immature neutrophils (bands).(2) Exclusion criteria included SIRS onset after 72h of initial hospital presentation, cardiovascular failure (systolic blood pressure ≤ 90 mmHg), respiratory failure (partial pressure of oxygen < 60 mmHg), renal failure (creatinine > 1.5 mg/dL), active peptic ulcer disease, pregnancy, active use of NSAIDs within 1 week of presentation, and allergy to NSAIDs. Participants were identified by daily electronic lipase laboratory alerts, and by care teams in the emergency department, medical floor, intensive care unit (ICU), and pancreatobiliary consult service, who directly contacted the study team. Eligibility was determined by the principal investigator (GP). Eligible subjects were invited for enrollment by the study coordinator (PP, IP). All enrolled participants provided written informed consent.

Statistical Considerations

Descriptive statistics are reported as absolute values (percentage), mean \pm standard deviation (SD), or median (interquartile range [IQR]), as appropriate. For the analysis of the primary endpoint, we used a two-sided Wilcoxon rank-sum test to analyze the difference in the change of SIRS scores between the treatment groups. Missing data of the primary outcome was handled using the last observation carried forward imputation method. Comparisons of baseline characteristics and secondary endpoints were evaluated using chi-square or Fisher's exact tests for categorical data and t-test or Wilcoxon rank sum test for continuous data, as appropriate. Kaplan-Meier methodology was used to estimate the overall risk of organ failure in each treatment group. The log-rank test was used to test the difference in risk of organ failure between treatment arms. Patients were followed up until date of organ failure or censoring. All analyses were performed according to the intention-to-treat principle. Per-protocol analysis was also performed. Statistical significance was defined as $P < 0.05$.